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Genetic Risk of Diverticular Disease Predicts Early Stoppage of Nicorandil

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Gastrointestinal fistulation has been widely reported as an adverse effect of nicorandil therapy in Europe. People who have underlying diverticular disease are most at risk of this side effect. In Western countries, diverticular disease is highly prevalent and can be clinically silent. This study aimed to identify diverticular disease genetic risk scores (GRSs) associated with early nicorandil stoppage, a surrogate marker for drug intolerance. A case-control study was carried out on 1,077 patients from the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) database. Cases were defined as having < 9 nicorandil prescriptions with no identifiable reason for stopping (n = 230). Controls had either ≥ 9 prescriptions, treatment continuation to death/study end or stoppage post-myocardial infarction. Two diverticular GRSs were created and used in logistic regression models. Isosorbide mononitrate was used as a control analysis. Patients with a raised diverticular GRS, based on 23 replicable loci, had increased risk of stopping nicorandil therapy early (univariate (odds ratio (OR) 2.26; P = 0.04], multivariate (OR 3.96; P = 0.01)). Similar trends were noted when using the full 42 variant diverticular score but statistical significance was not reached. The isosorbide control analysis did not reach statistical significance. Our analysis demonstrates a novel positive association between a raised diverticular GRS and early stoppage of nicorandil therapy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Patients with diverticular disease are seven times more likely to develop a fistula when taking nicorandil. In the Western world, ~ 50% of those aged over 60 years are predicted to have diverticular disease although many will have no symptoms, hence it would be beneficial to have a method of identifying people at higher risk for diverticular disease without colonoscopy.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ To establish whether the use of diverticular disease genetic risk scores (GRSs) could predict nicorandil intolerance, measured by early nicorandil stoppage.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study shows that a raised diverticular disease GRS is associated with early nicorandil stoppage.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Formal screening, for example, using colonoscopy, for diverticular disease is not currently undertaken prior to the initiation of nicorandil therapy. Our findings could provide clinicians with a means to prospectively identify those most at risk of nicorandil's adverse effects, allowing an alternative anti-anginal therapy to be offered.

Nicorandil is an anti-anginal agent recommended by European Society of Cardiology guidelines[1] as second-line therapy after beta blockers, calcium channel blockers, and long-acting nitrates. There is, however, increased recognition of side effects associated with nicorandil, in particular skin, mucosal, and gastrointestinal ulcers, which may progress to perforation, hemorrhage, fistula, or abscess.[2] Individuals with diverticular disease are seven times more likely to develop a fistula when taking nicorandil.[3] However, many patients with diverticular disease are asymptomatic, therefore, identification of patients at high-risk for developing gastrointestinal side effects with nicorandil use is difficult.

One potential approach to predict the risk of an off-target adverse drug effect is to study the patient's genetic profile. In support of this approach is identification of the SLCO1B1 variant that is associated with statin intolerance[4] and the rs3788853 variant of XPNPEP2 that may be associated with angiotensin-converting enzyme inhibitor-related angioedema.[5] Recent genomewide association studies have identified genetic variants associated with diverticular disease.[6] We hypothesized that patients at increased genetic risk of diverticular disease are more likely to develop adverse drug effects from nicorandil requiring treatment cessation. This study aimed to identify genetic risk scores (GRSs) associated with early nicorandil stoppage, a surrogate marker for drug

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intolerance. As a control, we have also evaluated the effect of these same GRSs on stoppage of isosorbide mononitrate.

METHODS

Study cohort

The cohort for this analysis is the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) database, details of which have been previously published.[7] In summary, the GoDARTS study recruited a population of 10,149 individuals with type 2 diabetes (T2D) and 8,157 controls without T2D. At recruitment, participants consented to access of their retrospective and prospective prescribing, biochemical, and baseline data for research purposes. This generated a comprehensive longitudinal electronic medical record for patients with T2D in the Tayside area with matched controls. Ethical approval was granted to the GoDARTS study by the Tayside Committee on Medical Research Ethics (REC reference 053/04) and the GoDARTS Access Committee approved our proposal (Ref GD0075).

Genotyping

Blood samples were obtained from patients who previously consented for DNA extraction and these samples were linked to their electronic medical records, as previously described. Genotyping was carried out across five platforms: Affymetrix Genome-Wide Human SNP Array 6.0, Illumina HumanOmni Express, SHAPEIT14, IMPUTE2, and various custom genotyping arrays from Illumina.[7]

Derivation of GRSs

A recent publication using UK Biobank data revealed 48 genetic variants that were associated with diverticular disease. Of these, 27 variants were replicated in a second European cohort.[6] In our analysis, two diverticular weighted GRSs were created: the first with replicable variants and the second with all diverticular associated variants included. Genetic data were available for 23 and 42 loci, respectively, from GoDARTS. To calculate the patient's weighted GRS, the natural log of the published odds ratio (OR) was determined for each effect variant contributing to the GRS. The sum of these values formed the patient's weighted GRS. The mean variant value for the cohort was used for missing variant data. Numbers of missing variants and the variants included in each score are shown in **Table S1**.

Outcomes

A pharmaco-epidemiological study, which used the GoDARTS database, was performed to examine associations between select GRSs and nicorandil intolerance, measured by early drug stoppage. The selection process to determine the cases and controls is described in **Figure 1**. The control group included patients who had their final nicorandil prescription in the 6 months preceding their death or the end of study data collection date. These patients were assumed not to have stopped nicorandil therapy due to intolerance. Additionally, patients who had their final nicorandil prescription in the 6 months before a myocardial infarction were assumed to have undergone revascularization therapy, no longer requiring an anti-anginal drug. These patients were added to the control group too, as they did not stop nicorandil due to adverse effects. The remaining patients were further stratified based on their number of nicorandil prescriptions to identify a case group who stopped nicorandil early. The median quantity of tablets per prescription was 84, and the most frequently prescribed dose was one tablet, twice a day. Nine prescriptions equate to roughly 1 year of treatment and any patient with nine or more prescriptions of nicorandil was added to the control group; the remaining patients were the cases ($n = 230$). Two patients were removed due to their final prescription being > 1 month after their death and one patient was removed due to missing baseline data.

As a further analysis, we also determined the association between the genetic risk scores and early stoppage of isosorbide mononitrate (ISMN). ISMN is another anti-anginal, which is rarely used for any other indications (similar to nicorandil), but has not been associated with gastrointestinal ulceration or diverticular disease, therefore, we would not expect there to be an association between the GRS and ISMN stoppage. GoDARTS data contained 3,003 patients who were prescribed ISMN. The nicorandil

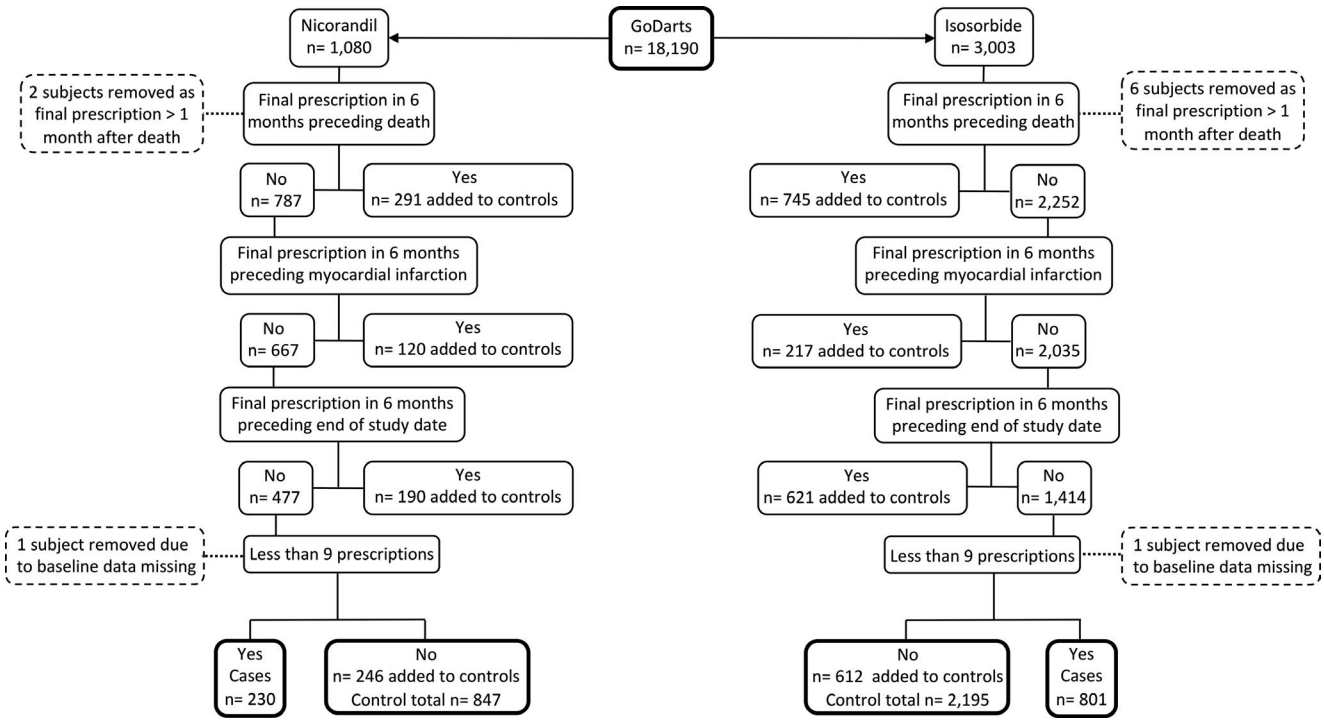

Figure 1 Selection process to determine the cases and controls.

and IMSN datasets were not exclusive and 911 patients were prescribed both drugs. The previously described methods were applied in the same way to this cohort. Six patients in this analysis were removed as their final prescription was > 1 month after their death and one patient was removed due to missing baseline data. In total, 2,996 patients who met the inclusion criteria were identified in the database, 801 cases and 2,195 controls (**Figure 1**).

Drug dose for both nicorandil and ISMN was categorized into four groups: low, medium, high, and unknown dose. The categories were created based on the spread of prescribing instructions available from the GoDARTS database. The total dose of two tablets a day was used as a medium dose for both cohorts. Any dose above or below this was classified as low or high, respectively. In both cohorts, any prescribing instruction that was not clear was classified as unknown. Tablet strength data was not available from GoDARTS.

Statistical analysis

The mean and SD were calculated for continuous covariates, and frequencies of each group were determined for categorical covariates (**Table 1**). Initial univariate logistic regression analyses were carried out among our dependent variable, early nicorandil stoppage, and the two weighted GRSs. Multivariate logistic models were subsequently generated with the following covariates: weighted GRS, age, sex, drug dose, and number of days between the first and last prescription. The multivariate analysis was repeated for each weighted GRS. The same process was carried out for our control ISMN cohort. Statistical analyses were conducted using R version 3.6.1 with statistical significance set at $P < 0.05$.

RESULTS

Baseline data are presented for both the nicorandil and ISMN analysis in **Table 1**. Univariate logistic regression models were used to test for associations between early nicorandil stoppage and each GRS independently. A positive univariate association was identified between the diverticular GRS comprised of 23 replicable loci and early stoppage of nicorandil (OR 2.26, 95% confidence interval (CI) 1.02–4.99, $P = 0.04$). The multivariate model adjusted for sex, age, number of days between first and last prescription, and drug dose showed an even stronger association (OR 3.96, 95% CI 1.35–12.17, $P = 0.01$).

The diverticular GRS comprised of all available 42 loci was also tested in a univariate model revealing again a positive association with early stoppage of nicorandil, but the association was weaker than the 23 variant model and did not reach statistical significance (OR 1.45, 95% CI 0.77–2.74, $P = 0.25$). The multivariate model increased the odds of early stoppage compared with the univariate model but did not reach statistical significance (OR 2.14, 95% CI 0.93–5.01, $P = 0.07$).

The same models were applied to the ISMN cohort that showed weaker associations in both scores, which were not statistically significant. The results for the univariate ISMN analyses are: 23 diverticular loci (OR 1.49, 95% CI 0.92–2.40, $P = 0.1$) and full 42 diverticular loci (OR 1.29, 95% CI 0.88–1.88, $P = 0.19$). The multivariate analyses results are: 23 diverticular loci (OR 1.99, 95% CI 0.95–4.17, $P = 0.07$) and full 42 diverticular loci (OR 1.19, 95% CI 0.67–2.13, $P = 0.55$).

DISCUSSION

The results of this analysis show, we believe for the first time, that increased genetic risk of diverticular disease predicts early stoppage of nicorandil treatment but not ISMN.

Nicorandil was first prescribed in Japan in 1984. In 1997, the first reports appeared of gastrointestinal ulceration and fistulation in association with nicorandil use.[3,8,9] General consensus from these initial case reports and observational studies was that the adverse effects cannot be predicted. However, more recent data have shown that individuals with diverticular disease are at an increased risk of bowel perforation[10] and are seven times more likely to develop a fistula.[3] These observational data support our analysis that

Table 1 Baseline characteristics of nicorandil and isosorbide mononitrate cohorts

	Nicorandil cohort			Isosorbide mononitrate cohort		
Characteristic	All *N* = 1077	Controls *N* = 847	Cases *N* = 230	All *N* = 2996	Controls *N* = 2195	Cases *N* = 801
Sex, *n* (%)						
Female	429 (39.8)	330 (39.0)	99 (43.0)	1,248 (41.7)	903 (41.1)	345 (43.1)
Male	648 (60.2)	517 (61.0)	131 (57.0)	1,748 (58.3)	1,292 (58.9)	456 (56.9)
Age, years	68.0 (10.5)	67.7 (10.4)	68.8 (10.7	64.7 (11.1)	65.3 (10.9)	63.3 (11.4)
Dose, *n* (%)						
Low	98 (9.1)	68 (8.0)	30 (13.0)	1,091 (36.4)	699 (31.8)	392 (48.9)
Medium	654 (60.7)	480 (56.7)	174 (75.7)	961 (32.1)	638 (29.1)	323 (40.3)
High	22 (2.0)	14 (1.7)	8 (3.5)	53 (1.8)	23 (1.0)	30 (3.7)
Unknown	303 (28.1)	285 (33.6)	18 (7.8)	891 (29.7)	835 (38.0)	56 (7.0)
Days between first and last prescription	1,999.3 (1,990.6)	2,485.9 (1,956.9)	207.7 (608.7)	2,864.1 (2,780.4)	3,784.7 (2,663.0)	341.4 (892.6)
Diabetes diagnosis, *n* (%)	817 (75.9)	659 (77.8)	158 (68.7)	2,137 (71.3)	1,628 (74.2)	509 (63.5)
23 variant diverticular GRS	−0.07 (0.18)	−0.07 (0.17)	−0.05 (0.19)	−0.07 (0.17)	−0.07 (0.17)	−0.06 (0.15)
42 variant diverticular GRS	0.14 (0.23)	0.14 (0.23)	0.16 (0.23)	0.14 (0.21)	0.14 (0.22)	0.15 (0.20)

Values are reported as the mean (SD), unless indicated otherwise.
GRS, genetic risk score.

an individual's genetic risk might be useful in identifying patients at high-risk of nicorandil-induced gastrointestinal side effects.

Scandinavian twin studies have shown that diverticular disease has a significant heritable component of up to 50%.[11–13] Epidemiological studies have estimated that 50% of those aged over 60 years old in the Western world have diverticular disease compared with a prevalence of < 0.5% in Asia.[14] This finding does not seem to be influenced by changes in environmental factors, demonstrated by migrant studies, suggesting that the difference in prevalence is mediated through a genetic mechanism.[15–17] The genomewide association studies showing associations to diverticular disease were completed in European cohorts and are likely to be specific to white patients. The genetic variance between populations may explain why there were no published reports of gastrointestinal adverse events associated with nicorandil use during the 10-year post-approval period in Japan. In France, nicorandil was approved for use in 1994 and the first report of nicorandil-induced mouth ulcerations was published 3 years later.[18]

Diverticula most often occur at vulnerable sites where blood vessels cross the colon muscle wall. It is hypothesized that in these outpouchings, nicorandil's toxic metabolites accumulate causing epithelial proliferation and subsequent tissue ulceration.[8] Additionally, it has been postulated that nicorandil releases proinflammatory nitric oxide, which may also trigger the development of fistulas among sigmoidal diverticula.[3]

The main clinical implication of our study is the potential for the use of a GRS to predict adverse side effects with nicorandil use. Genotyping can now be undertaken for £30/$40 allowing for the future development of a clinical decision support tool to guide prescribing.[19] If patients were found to have an elevated weighted GRS based on our 23 variant score, shown in **Table S1**, we propose that an alternative anti-anginal is prescribed. Importantly, this weighted GRS was not associated with early stopping of ISMN.

There are potential limitations to our study, mainly contributed to the challenges of using retrospective prescribing data. Only 19 patients in the nicorandil group had International Classification of Diseases codes for any form of ulceration or fistula, seven of which continued their treatment until death, end of study date, or stopped due to myocardial infarction. Additionally, the use of GoDARTS data does not permit review of individual patient notes. Therefore, information regarding drug dosing and exact duration of treatment was inaccessible. Assumptions also had to be made based on the general prescribing prediction that nicorandil is rarely stopped once started. In addition, as highlighted in **Table S1**, not all variants had been genotyped for every patient and the mean variant value had to be substituted in a number of instances. Despite these obstacles we have identified a GRS that is strongly associated with stoppage of nicorandil, providing for the first time a predictive tool to reduce the risk of adverse effects.

CONCLUSION

Our analysis has identified that use of a GRS for increased likelihood of diverticular disease was associated with early stoppage of nicorandil treatment. This highlights the potential for use of a pharmacogenomic strategy in prescribing nicorandil, which could be an additional tool to help clinicians identify the optimal prescribing choice for each individual patient.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

J.D.N., I.R.M., and C.C.L. wrote the manuscript. C.C.L., I.R.M., E.R.P., C.N.A.P., and A.S.D. designed the research. J.D.N., I.R.M., and C.C.L. performed the research. J.D.N. and I.R.M. analyzed the data.

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